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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,460	03/23/2001	Shanaz H. Dairkee	CPMC-010/00US	6434

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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,460	DAIRKEE ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *18-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/23/03 & 7/9/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, Claims 1-17 in the reply filed on July 12, 2004 is acknowledged. Accordingly claims 18-22 has been withdrawn from consideration as being drawn to a non-elected invention.

2. Applicant's preliminary amendment filed on August 13, 2002 is acknowledged and has been entered.

Specification

2. The disclosure is objected to because of the following informalities:

(a) The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at page 11, line 22. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

(b) The specification contains underlining at pages 2, lines 1, 14, 15, 19-21 and page 3, lines 1, 3, 4, 6-8, 10, 12, and 18, which are not intended to encompass an amendment (see 37 CFR 1.121 (e)(2)(ii)). It is suggested removing the underlining from the specifications. To indicate the amendment to the specification, words wherein the underline was remove should be enclosed in double brackets [[ ]].

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 8-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining the likelihood of tumor reoccurrence in a patient previously diagnosed with a breast tumor or method of determining post-surgical treatment for a breast cancer patient or method of identifying a patient as being at risk for breast cancer by analyzing breast tissue cell sample for loss of heterozygosity (LOH) at chromosomal locus 3p24.3, it does not reasonably provide enablement for a method for determining the likelihood of tumor reoccurrence in a patient previously diagnosed with a breast tumor or method of determining post-surgical treatment for a breast cancer patient or method of identifying a patient as being at risk for breast cancer by analyzing a tissue cell sample for the level of expression of thyroid hormone receptor beta 1 (TRβ1) gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is "undue". These factors include but are not limited to: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented in the specification, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the unpredictability of the art and (8) the breadth of the claims. (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)) *(MPEP 2164.01(a))*.

The claimed invention is drawn to a method for determining the likelihood of tumor reoccurrence in a patient previously diagnosed with a breast tumor, or a method of determining post-surgical treatment for a breast cancer patient said method comprising (1) providing a target cell sample from said patient, wherein said target cell sample comprises morphologically normal cell from tissue peripheral to the carcinoma cells; analyzing the target cell sample for the level of expression of thyroid hormone receptor beta 1 compared to a control cell sample; and classifying a target cell sample having a lower level of expression thyroid hormone receptor beta 1 compared to the control cell sample as positive, wherein a positive sample indicates a greater likelihood of tumor reoccurrence or that more aggressive post-surgical treatment is required.

The claimed invention is also drawn to a method of identifying a patient as at risk for breast cancer, said method comprising (1) obtaining a breast tissue cell sample from said patient; (2) analyzing the breast tissue cell sample for the level of expression of thyroid hormone receptor beta 1 compared to a control cell sample; and classifying a patient whose breast tissue cell sample have a lower level of expression of thyroid hormone receptor beta 1 (TRβ1) compared to a control cell sample as at risk for breast cancer.

The specification at page 10 discloses that Applicant have found that the LOH at 3p24.3 is correlated with a decrease in the expression of the TRβ1 gene in morphologically normal cells. The specification discloses that the decrease in expression is not due entirely to the deletion of the gene as one copy of the gene is still present on the remaining allele. The specification teaches that rather, the decrease in expression can be attributed to an increase in the methylation of the TRβ1 promoter. Despite extensive statements that the expression of TRβ1 gene is correlated with LOH at 3p24.3, there is no substantial data which supports applicants claims that

analysis of the expression of the TRβ1 gene is indicative of a likelihood of breast tumor reoccurrence in a patient or is indicative of a determination for post-surgical treatment for a breast cancer patient or alternatively, is indicative of identifying a patient as at risk for breast cancer. The data in the specification appears to be speculative at best, For example, at page 20, the specification teaches that the transcript levels in normal breast organoids prior to cell culture and in cultures of the same specimen at passage 2 showed close similarity. The specification further discloses that breast cancer cell lines displayed a range of TRβ1 gene expression. The specification at page 21 teaches that TRβ1 transcript levels below those found in non-cancerous breast epithelial cultures from a non-malignant reduction mammoplasty specimen was observed in 3/10 (about 30%) breast cancer lines examined and were not detectable in cell lines DU4475, MDA 435 and SKBR3. The specification further states that homozygous deletions of TRβ1 were not detected in any breast cancer cells line (page 21). There is no information provided that suggests that the undetected or low levels of expression of the TRβ1 gene are correlative to the LOH in breast tumor. While the specification and prior art supports the TRβ1 gene being present at chromosomal locus 3p24.3, undue experimentation would be required of the skilled artisan to determine whether a change in expression level of the TRβ1 gene is correlative to or indicative of breast tumor reoccurrence, or the determination of post surgical treatment or diagnosis of a risk of breast cancer. No guidance is given to in the specification teaching the skilled artisan how to determine significant expression level changes of the TRβ1 gene, as indicative of a breast tumor or a breast cancer marker. Likewise, the methylation data provided in the specification is inconclusive and does not provide any further guidance to suggest Applicant's claims in claims 8-17. The specification has provided little to no guidance beyond

the mere presentation of the methylation state of the TRβ1 gene in breast cell lines. A large quantity of experimentation would be required by the skilled artisan to determine sample size and monitor over a period of years the expression level of the TRβ1 gene as it relates to the breast tumor reoccurrence. One of skill in the art would have to establish if the methylation state of the TRβ1 gene *or* the expression of the TRβ1 gene is most critical to the identification of risk of breast cancer and/or reoccurrence of breast tumors. Such trial and error is considered undue and according to MPEP 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objective may be an issue to be considered in determining the quantity of experimentation needed".

Due to the large quantity of experimentation necessary to establish how the expression of the TRβ1 gene is correlative to breast tumor reoccurrence and risk of breast cancer, the lack of direction and guidance present in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention and the breadth of the claim which fails to recite more specific evidence for the role of the TRβ1 gene in breast cancer diagnosis, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102/35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Deng et al. (Science, Vol. 272, pages 2057-2059, 20 December 1996). Regarding claims 1, 2, 4-6, Deng et al teach a method comprising the steps of providing a target cell sample from a patient wherein said target cell sample comprises morphologically normal breast cells associates with a tumor, analyzing the target cell sample from a patient for loss of heterozygosity at chromosomal locus 3p22-25, classifying samples as having LOH at chromosomal locus 3p22-25 as positive, wherein a positive sample may indicate a risk of breast cancer, a likelihood of tumor reoccurrence, or more aggressive post surgical treatment (see entire reference, especially, Figure 2, Table 1 and page 2059, col. 2, last full paragraph). The preceding rejection is based on the judicial precedent following *In re Fitzgerald*, 205 USPQ 594 because the reference is silent with regards to the chromosomal locus being at 3p24.3. However, this locus is deemed to be inherent by the reference of Deng et al. in the teaching that cells were examined for LOH at chromosome 3p22-25 which encompasses the locus 3p24.3. Additionally, Deng et al analyzed the same locus EABMD and EABH) noted by Applicant at page 17, line 1 to be within 3p24.3 (see figure 2, fourth line from bottom of legend). The Burden is on Applicant

to establish that the locus of the prior art is different from that of the instant invention.

Regarding claim 3, Deng et al teach the method of claim 1, wherein the patient has undergone a surgical procedure (mastectomy) to treat said previously diagnosed cancer (page 2058, col. 3, line 2 from bottom of col.).

Regarding claim 7, Deng et al teach the method of claim 6, wherein said breast tissue is a breast tissue biopsy tissue (page 2059, reference note number 14).

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

CYNTHIA WILDER
PATENT EXAMINER
9/29/2004